## REMARKS

Claims 12-14, 16, 23-25, 27-29, 31, 32-34 are pending in the subject application. Claims 1-11 have been canceled.

## DOUBLE PATENTING

The Examiner provisionally rejects claims 12-14, 16, 23-25, 27-29, 31, and 32-34 under the judicially-created doctrine of obvious-type double patenting over co-pending application 09/842,111 in view of Gonzalez et al. (U.S. 6,015,673). Applicants respectfully submit that the present claims are not obvious in light of Gonzalez, as demonstrated below. However, if the Examiner still maintains the obvious-type double patenting rejection over co-pending application 09/842,111, Applicant will file a terminal disclaimer pursuant to 37 C.F.R. §§1.130(b) and 1.312, upon a showing by the Examiner that the claims at issue are in condition for allowance, and if the 09/842,111 claims have issued.

## REJECTION UNDER 35 U.S.C. § 103(a)

Claims 12-13, 16, 23, 24, 27, 28, 31, 32 and 34 have been rejected under 35 U.S.C.§103 (a) over Gonzalez *et al.* (U.S. Patent 6,015,673) in view of Willhauck *et al.* (Biotechniques (1998) 25:656-659) and further in view of Buck *et al.* (Biotechniques (1999) 27 (3): 528-536) and further in view of Stanta *et al.* (Biotechniques (1991) 11(3): 303, 306, and 308).

Applicants respectfully disagree as Gonzalez does not teach each and every element of the claimed invention and taken with Willhauck and Stanta does not make up for these deficiencies. For instance, the present claims involve specific oligonucleotide sequences capable of amplifying DPD mRNA from FPE tissue. Gonzalez does not teach or suggest this. The Examiner states that the SEQ ID NO: 5 of Gonzalez is "substantially identical" to one of the claimed oligonucleotides. However, there is no teaching or suggestion of the four complete claimed primer sequences. Nor is there teaching or suggestion of the necessity for nucleotide sequences to robustly provide reproducible quantitation of DPD expression in samples isolated from FPE tissue and not to simply have the ability to bind to the DPD gene.

As provided in the Declaration of Kathleen Danenberg, even though a primer may bind to the DPD gene, they do not necessarily have the ability to detect DPD expression at such low levels. The present invention provides oligonucleotide primer sequences that have been proven preferable to DPD primer sequences of a research diagnostic company. To say that all primer pairs should be expected to work fails to address the facts of the present invention that is that

even among primer pairs developed in-house at RGI, as discussed in Kathleen Danenberg's Declaration, half of the primer pairs failed to detect DPD expression in tissue samples. Furthermore, even among the successful primer pairs there is a marginal degree of enhanced specificity in detection of low DPD levels of expression. Merely alleging tat the primer SEQ ID NO: 5 of Gonzalez has a 73% homology over the claimed sequence does not address the fact that the primers of the present invention are not obvious in light of the findings presented in the Declaration attached hereto. Furthermore, even among the successful primers pairs of the invention there is a marginal degree of enhanced specificity in detection of low DPD levels of expression.

As discussed in the Declaration of Kathleen Danenberg, and as provided in the specification of the present invention, it is important to be able to detect patients with very low DPD levels undergoing 5-FU based therapy due to the potential of life-threatening toxicity. Thus, as illustrated by the data in the Declaration, the oligonucleotide primers of the present invention are the most effective at detection of low levels of DPD in various tissue samples and provide an needed improvement over other DPD primers.

Applicants respectfully disagree as Gonzalez does not teach each and every element of the claimed invention and Willhauck, Buck and Stanta do not make up for these deficiencies which are characterized as variations that are "routine optimization." The fact that Gonzalez teaches a method of freezing or fixing a sample for detection is irrelevant, as the present claims involve fixing a portion of a tumor sample in paraffin. Gonzalez does not teach or suggest this. The present claims involve isolating mRNA from the fixed and paraffin embedded (FPE) tumor tissue. Gonzalez does not teach or suggest this. The present claims involve amplifying mRNA from the FPE tumor tissue. Gonzalez does not teach or suggest this. The present claims also involve comparing expression levels of DPD in the amplified mRNA from the FPE tumor sample with the mRNA from an internal control gene. Gonzalez does not teach or suggest this. The present claims also involve the use of claimed primers for amplifying the mRNA. Gonzalez does not teach the claimed primers, regardless of the homology of those primers identified in Gonzalez. Willhauck does not teach or suggest these missing elements and does not make up for the shortcomings of Gonzalez. For example, the Examiner cites Willhauck for teaching comparing the amount of the target gene to an internal gene, including B-actin. Willhauck, however, actually teaches away from the use of housekeeping genes, such as GAPDH and B-actin. (See page 656 column 1). Specifically, Willhauck states that such housekeeping genes are "not suitable for reliable detection of tumor targets with low mRNA expression levels." Thus,

applicants respectfully assert that the combination of Gonzalez and Willhauck does not teach nor suggest the claimed invention and therefore does not render the claims obvious.

Furthermore, in response to the Examiner's assertion that one would have a reasonable expectation of success in using the primers of Gonzalez based on the teaching of Buck, as addressed above, the applicants respectfully disagree. As provided in the Declaration of Kathleen Danenberg, again, even though a primer may bind to the DPD gene, they do not necessarily have the ability to detect DPD expression at such low levels. The present invention provides oligonucleotide primer sequences that have been proven preferable to DPD primer sequences of a research diagnostic company. To say that all primer pairs should be expected to work fails to address the facts of the present invention that is that even among primer pairs developed in-house at RGI, as discussed in Kathleen Danenberg's Declaration, half of the primer pairs failed to detect DPD expression in tissue samples. Indeed, Buck teaches that it is only with optimal sequencing conditions with highly pure template and primer would you expect the results presented in the article (see page 535, column 2, which notes that the plasmid template was purified by double banding in CSCl-ethidium bromide isopycnic density gradients). Thus, in the absence of these factors, one skilled in the art would not be guaranteed a reasonable expectation of success. Even more pointedly, as demonstrated by Applicants' results, not even all of the primers developed by the applicant was able to detect low levels of DPD expression from FPE tissues. The Examiner seems to be completely ignoring the fact that the claimed methods and primers must be capable of "amplifying mRNA. . ." Even if Buck were to teach optimal conditions for sequencing primers, there is no relationship between ability of a primer to be capable of amplifying DPD mRNA from FPE tissue and ability of a primer to sequence DNA. Simply because Buck allegedly teaches optimization of sequencing primers, there is no teaching or suggestion that choosing primers for amplifying DPD mRNA from FPE tissue is similarly a simple optimization. The submitted Declaration of Kathleen Danenberg shows just that. Therefore, applicants respectfully assert that the combination of Gonzalez and Buck does not teach nor suggest the claimed invention and therefore does not render the claims obvious. Accordingly, applicants respectfully request withdrawal of this ground of rejection.

In response to the Examiner's assertion that it would be obvious to one skilled in the art to combine the teaching of Gonzalez with Willhauck, Buck and Stanta, as addressed above, the applicants respectfully disagree. Applicants argue that as with Willhauck, Stanta actually teaches away from the claimed invention and, thus, one would not be motivated to combine the teachings of Gonzalez with the teachings of Stanta to arrive at the presently claimed invention. For example, the Examiner cites Stanta for teaching a chaotropic agent, yet Stanta, on page 307

column 1, characterizes the second step of the method as teaching "a proteolysis step with a high concentration of proteinase K in the presence of 1 M guanidinium thiocyanate" to allow for efficient RNA extraction without further degradation. In contrast, the claimed method uses a chaotropic agent (without a high concentration of proteinase K) at higher temperatures for shorter times to extract mRNA from fixed paraffin embedded samples. Additionally, the allegation that 45° C was "about 50 to about 120 °C" or "about 75 to about 120 °C" is not accurate. Based upon the fragility of RNA, one skilled in the art at the time of the invention would not consider an increase in the temperature or the dramatic increase in time of incubation during RNA extraction as "routine optimizable variations" as the Examiner alleges. Rather, Applicants argue that one of the fundamental inventive concepts of the Applicants patent application is the very idea that by raising the temperature, the RNA would not be destroyed and one could obtain a better yield of RNA from FPE tissue samples. Thus, applicants respectfully assert that the combination of Gonzalez and Stanta does not teach nor suggest the claimed invention and therefore does not render the claims obvious. Accordingly, applicants respectfully request withdrawal of this ground of rejection.

Claims 14, 25, 29 and 33 have been rejected under 35 U.S.C.§103 (a) over Gonzalez et al. (U.S. Patent 6,015,673) in view of Willhauck et al. (Biotechniques (1998) 25:656-659), further in view of Buck et al. (Biotechniques (1999) 27 (3): 528-536) , further in view of Stanta et al. (Biotechniques (1991) 11(3): 303, 306, and 308) and further in view of Johnston, et al. (Cancer Research, 55 (7): 1407-12 (April 1995)).

As previously stated, Applicants respectfully disagree as Gonzalez does not teach each and every element of the claimed invention and Willhauck, Buck, Stanta and Johnston do not make up for these deficiencies. As noted above, Willhauck actually teaches away from the use of housekeeping genes, such as GAPDH and B-actin. Thus, applicants respectfully assert that one skilled in the art would not be motivated to combine Gonzalez and Johnston, in view of Willhauck, and therefore, this combination does not teach nor suggest the claimed invention and therefore does not render the claims obvious. Accordingly, applicants respectfully request withdrawal of this ground of rejection.

## CONCLUSION

It is believed that the present claims are in conditions for allowance and earnestly request allowance. Extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefore (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 11-0600. The Office is hereby authorized to charge any additional

fees or credit any overpayments under 37 C.F.R. 1.16 or 1.17 to Kenyon & Kenyon Deposit Account No. 11-0600. The Examiner is invited to contact the undersigned at 202-220-4258 to discuss any matter concerning this application.

Respectfully submitted,

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